USING COGNITIVE ASSESSMENT TOOLS REMOTELY TO DETECT MCI IN THE CONTEXT OF COVID AND POTENTIAL USE WITH ANTI-AMYLOID THERAPIES

Serge Gauthier, C.M., C.Q., MD, FRCPC
Emeritus Professor in Neurology and Psychiatry, McGill University
POTENTIAL CONFLICTS OF INTEREST

Member of scientific advisory boards with Advantage Therapeutics, Alzheon, Amyriad Therapeutics, Biogen, Cerveau Technologies, Lundbeck, MoCA Test Inc., TauRx
CONCLUSIONS

• The diagnosis of MCI and dementia due to AD is becoming biological
• The COVID-19 pandemic has accelerated the use of telemedicine, including remote cognitive assessments
• MCI due to AD has become a target for disease modifying therapies
CONCLUSIONS

• The diagnosis of MCI and dementia due to AD is becoming biological but should done in symptomatic people with demonstrated cognitive decline

• The COVID-19 pandemic has accelerated the use of telemedicine, including remote cognitive assessments –

• MCI due to AD has become a target for disease modifying therapies
CONCLUSIONS

• The diagnosis of MCI and dementia due to AD is becoming biological but should done in symptomatic people with demonstrated cognitive decline.

• The COVID-19 pandemic has accelerated the use of telemedicine, including remote cognitive assessments – possibly a golden age for remote cognitive screening for MCI.

• MCI due to AD has become a target for disease modifying therapies.
CONCLUSIONS

• The diagnosis of MCI and dementia due to AD is becoming biological but should done in symptomatic people with demonstrated cognitive decline.

• The COVID-19 pandemic has accelerated the use of telemedicine, including remote cognitive assessments – possibly a golden age for remote cognitive screening for MCI.

• MCI due to AD has become a target for disease modifying therapies and will require in-person and remote cognitive & functional follow-up.
World Alzheimer Report 2021
Journey through the Diagnosis of Dementia

www.alzint.org/worldreport
Six sections:

• **Part I**: Clinical assessment
• **Part II**: Laboratory tests
• **Part III**: Personal testimonies
• **Part IV**: Formulation of diagnosis
• **Part V**: Particular circumstances
• **Part VI**: The future of the diagnosis of dementia
Expert essays: To encapsulate a broad range of knowledge, healthcare professionals were invited to submit essays within their field of expertise.

Surveys: The three surveys were conducted concurrently between March and June 2021, targeting people living with dementia and carers, clinician’s and Alzheimer and dementia associations

Testimonies: Individual case studies were requested from people living with dementia and eight are included covering all WHO regions. A larger set of videos, accompanying this report can be found on ADI's YouTube channel
The report contains survey data from a total of 3,431 respondents consisting of:

- 1,111 multidisciplinary clinicians in 108 countries (62% from high income countries and 38% from low- and middle-income countries)
- 205 people with dementia and 2122 carers in 83 countries
- 101 Alzheimer’s and dementia associations from around the world
The report contains survey data from a total of 3,431 respondents consisting of:

- 1,111 multidisciplinary clinicians in 108 countries (62% from high income countries and 38% from low- and middle-income countries)
- 205 people with dementia and 2122 carers in 83 countries
- 101 Alzheimer’s and dementia associations from around the world
Cognitive assessments are required for the diagnosis of dementia and to track changes over time.

The cognitive screening tests most used by clinicians worldwide are the Mini Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA).

Tests that overcome the influence of language differences are needed, such as the Visual Cognitive Assessment Test (VCAT).

As a result of the COVID-19 pandemic, many clinicians have incorporated telemedicine into their practice.
POLLING QUESTION NO 1: TRUE OR FALSE?

In the survey conducted among clinicians worldwide towards WAR2021 on the diagnosis of dementia, most answered that they do not want to use remote cognitive assessments.
If there were adequately validated clinical tests for cognition that can be done remotely (phone, tablet, computer), would you likely use them in your clinical practice?

- No, because it has not been around long enough to be sure of its utility
- No, because it involves extra time to explain and perform the test
- No, because the cognitive test is not sufficient to assess the overall clinical picture
- No, because there is no payment for reviewing the results of this test
- No, because they rarely take into account cultural and language issues
- Yes, for patients with dementia who cannot come in person
- Yes, for patients with dementia who need a routine follow-up

Lower Income

High Income
POLLING QUESTION NO 1: TRUE OR FALSE?

In the survey conducted among clinicians worldwide towards WAR2021 on the diagnosis of dementia, most answered that they do not want to use remote cognitive assessments

FALSE
Recommendations

• Better training, education and time allocation is required in primary healthcare in diagnosis, to combat lack of skills and confidence and to remove the counter-productive time pressure on primary care doctors when dealing with a complex and sensitive diagnosis and disclosure.

• Healthcare systems must invest in and improve diagnostic capabilities, moving towards precision diagnosis, to eradicate high levels of misdiagnosis.
Plasma p-tau is a novel, promising blood-based biomarker for Alzheimer’s disease

Plasma p-tau levels are increased in AD

- Aβ- Cognitively unimpaired N=244
- Aβ- Mild cognitive impairment N=86
- Aβ+ Cognitively unimpaired N=77
- Aβ+ Mild cognitive impairment N=92
- Aβ+ Alzheimer disease dementia N=121

Approximative ordering of Alzheimer’s disease biomarker changes during the disease course

- Aβ42 (CSF and plasma)
- Tau PET
- MRI measures of atrophy
- Global cognition and ADL function

Biomarker abnormality

- Restricted MTL tau pathology
- Cortical Aβ pathology starts
- Increased phosphorylation and secretion of soluble tau
- Widespread cortical PHF tau pathology and acceleration of neurodegeneration

Detection threshold

Figure adapted from Palmqvist S, et al. JAMA. 2020;324:772–781.1

Figure adapted from Hansson O. Nat Med. 2021;27:954–963.2

Recommendations

- National awareness raising campaigns must address the stigma surrounding dementia, especially in some low-income countries where up to 90% of cases go undiagnosed and actively promote awareness of the warning signs, in line with action area two of the WHO Global action plan on dementia.

- Best practice in assessment must be recognised as a combination of cognitive testing, backed up by scan and/or CSF testing, plus preparedness and readiness to embrace emerging biomarkers.

- Improved access to scanner technology required for confirmatory diagnosis, for access to emerging treatments and ongoing monitoring, with equivalent specialist training.
Figure. Amyloid positron emission tomography (PET), tau PET, and MRI from a man, age 80, with mild dementia (CDR 1) after a gradual cognitive decline over 5 years and clinical diagnosis of probable AD. The amyloid PET is read as negative, the tau PET positive on the temporal lobe, precuneus, inferior parietal cortex, orbitofrontal cortex, and amygdala (Braak V). The MRI shows mild general and hippocampal atrophy (Scheltens 4-5), White matter hyperintensities (WMH) are limited to the periventricular regions (Fazekas 1). This individual has a neurofibrillary tangle predominant dementia.
Recommendations

- Clinicians must become aware and better informed about information, support and planning available via national Alzheimer and dementia associations and the vital role they play in pre and post diagnostic support.

- Further build on the innovative, often technology-based approaches, including telemedicine, which evolved rapidly during the COVID-19 pandemic, and research how these might best supplement, but not replace, future cognitive assessment, while acknowledging the benefits for remote or rural communities or for those unable to travel safely.

Maiya R. Geddes¹,²,³  |  Megan E. O’Connell⁴,⁵  |  John D. Fisk⁶,⁷,⁸  |  Serge Gauthier⁵  |  Richard Camicioli⁹  |  Zahinoor Ismail¹⁰,¹¹  |  for the Alzheimer Society of Canada Task Force on Dementia Care Best Practices for COVID-19
POLLING QUESTION NO 2: TRUE OR FALSE?

The same ethical principles apply to telemedicine and remote cognitive assessments as for in-person encounters.
The same ethical principles apply to telemedicine and in-person encounters
Ethical adoption of technology
Fidelity: The interests and welfare of patient come first
Verbal consent – Transparent disclosure of rationale and limitations
Handling imminent risk
Minimize obtrusiveness
  – Telephone vs videoconference
Verbal and non-verbal cues conveying empathy
  – Clinician training
The same ethical principles apply to telemedicine and remote cognitive assessments as for in-person encounters.

TRUE
POLLING QUESTION NO 3: TRUE OR FALSE?

There are no functional and behavioral scales usable for remote assessments in MCI.
Remote assessment of Affect, Behavior and Function

- **Neuropsychiatric symptoms** (e.g., Neuropsychiatric Inventory Questionnaire [NPI-Q]; Mild Behavioral Inventory Checklist [MBI-C])

- **Affect**
  - Depression (e.g., Cornell Scale for Depression in Dementia [CSDD]; Patient Health Questionnaire-9 [PHQ-9])
  - Anxiety (Rating Anxiety in Dementia [RAID] – sensitive; Penn State Worry Questionnaire - specific)

- **Function** (e.g., AD8; Informant Questionnaire on Cognitive Decline in the Elderly [IQCODE]; Quick Dementia Rating System; FAQ; Lawton-Brody IADL; 4-item IADL scale; Amsterdam IADL questionnaire)

- **Sleep** (e.g., Mayo Sleep Questionnaire)

Geddes et al., 2020; Geddes et al., 2021 (accepted)
POLLING QUESTION NO 3: TRUE OR FALSE?

There are no functional and behavioral scales usable for remote assessments in MCI.

FALSE
Hypothetical treatment responses in AD

- Early diagnosis
- Mild-moderate
- Severe

Gauthier (1996)
Therapy in AD: The first hundred years and looking forward………

- **The cholinergic hypothesis**
- Memantine NMDA Uncompetitive Receptor Antagonist
- Acetylcholinesterase inhibitors
- First Disease Modifying Rx? Amyloid and tau lowering? Next generation targets?
SYMPTOMATIC DRUGS FOR DEMENTIAS

- Antidepressants (ex. escitalopram)
- Cholinesterase inhibitors (donepezil, rivastigmine, galantamine)
- NMDA receptor antagonist (memantine)
- Atypical antipsychotics (risperidone, olanzapine, quetiapine)
NATURAL HISTORY OF AD AND CURRENT Rx

No standard drug therapy

Normal

MCI

Antidepressants Cls

Early

Cls Memantine

Moderate

Memantine Atypical neuroleptics

Severe

Memantine Atypical neuroleptics

Terminal
Hypothetical treatment responses in AD

- Early diagnosis
- Mild-moderate
- Severe

MMSE

- 30
- 25
- 20
- 15
- 10
- 5
- 0

Onset of treatment

Gauthier (1996)
Alzheimer’s disease exists on a spectrum from minimal symptoms to dementia.

- Increasingly severe phenotype
- Biomarkers assist in identifying the underlying pathology
- Biomarker changes may precede clinically detectable changes

© JL Cummings, 2008
PATHOLOGIES ASSOCIATED WITH AD

AGE

β-amyloid deposition

Microglial activation

NFTs

Neuronal loss

Symptoms
TESTABLE HYPOTHESIS

• Beta-amyloid deposition
• Tau hyperphosphorylation
• Excessive brain inflammation
β-Amyloid treatment strategies under study

APP gene

Production

APP

Antisense

Secretase inhibitors & modulators

Aβ Monomer

Immunotherapy

Aβ Oligomer

Aggregation

Aβ Fibril

Deposition

Fibrillogenesis modulators

Diffuse Plaque

Anti-inflammatory

Senile Plaque
## Amyloid Plaque Reduction with Aducanumab

### Analyses based on observed data. PD analysis population is defined as all randomized subjects who received at least 1 dose of study medication and had at least 1 post-baseline assessment of the parameter.

### Placebo (n=34, 34, 21) vs Aducanumab 1 mg/kg (n=26, 26, 21)
- Aducanumab 3 mg/kg (n=29, 27, 26)
- Aducanumab 6 mg/kg (n=23, 23, NA)
- Aducanumab 10 mg/kg (n=28, 27, 21)

---


---

Aducanumab is an investigational drug and not approved in Canada
Aducanumab Effect on CDR-sb

CDR-sb is an exploratory endpoint. Analyses based on observed data. ANCOVA for change from baseline with factors of treatment, laboratory ApoE ε4 status (carrier and non-carrier), and baseline CDR-sb. Efficacy analysis population is defined as all randomized subjects who received at least 1 dose of study medication and had at least 1 post-baseline questionnaire assessment.

Aducanumab is an investigational drug and not approved in Canada.
EMERGE: Amyloid PET showed dose- and time-dependent reduction in β-amyloid pathology with aducanumab

The amyloid level in the high dose aducanumab group was reduced to ~25 centiloid units at Week 78.

Baseline SUVR (centiloid)
- 1.394 (88.0)
- 1.383 (85.3)

Difference vs placebo SUVR (centiloid)
-0.179 (-41.3)
-0.278 (-64.2)

Adjusted mean change from baseline, composite SUVR, ±SE

Avec la permission et gracieuseté de BIOGEN
EMERGE: Longitudinal Change from Baseline in CDR-SB

The primary endpoint of change from baseline in CDR-SB at Week 78 was met

Placebo
Low-dose aducanumab
High-dose aducanumab

Week 78
High dose
Low dose
n=543  n=547

% Difference from placebo at Week 78 (95% CI) p value

Avec la permission et gracieuseté de BIOGEN
**EMERGE: Clinical Endpoints at Week 78**

High dose aducanumab met all clinical endpoints assessing cognition, function and behavior at Week 78.

**Primary endpoint**

<table>
<thead>
<tr>
<th>Metric</th>
<th>Difference from Placebo (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDR-SB</td>
<td>0.1 (0.00, 0.25)</td>
<td>0.0493</td>
</tr>
<tr>
<td>MMSE</td>
<td>0.6 (0.00, 1.13)</td>
<td>0.0493</td>
</tr>
<tr>
<td>ADAS-Cog 13</td>
<td>-0.7 (-1.36, 0.34)</td>
<td>0.0097</td>
</tr>
<tr>
<td>ADCS-ADL</td>
<td>1.7 (0.75, 2.74)</td>
<td>0.0008</td>
</tr>
</tbody>
</table>

**Secondary endpoints**

<table>
<thead>
<tr>
<th>Metric</th>
<th>Difference from Placebo (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDR-SB</td>
<td>-0.39 (-0.69, -0.09)</td>
<td>0.0120</td>
</tr>
<tr>
<td>MMSE</td>
<td>-0.7 (-1.36, 0.34)</td>
<td>0.0097</td>
</tr>
<tr>
<td>ADAS-Cog 13</td>
<td>-1.2 (-2.3, 0.1)</td>
<td>0.0215</td>
</tr>
<tr>
<td>ADCS-ADL</td>
<td>0.7 (0.27, 1.73)</td>
<td>0.1962</td>
</tr>
</tbody>
</table>

**Tertiary endpoint**

<table>
<thead>
<tr>
<th>Metric</th>
<th>Difference from Placebo (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CDR-SB</td>
<td>-0.39 (-0.69, -0.09)</td>
<td>0.0120</td>
</tr>
<tr>
<td>MMSE</td>
<td>-0.7 (-1.36, 0.34)</td>
<td>0.0097</td>
</tr>
<tr>
<td>ADAS-Cog 13</td>
<td>-1.2 (-2.3, 0.1)</td>
<td>0.0215</td>
</tr>
<tr>
<td>ADCS-ADL</td>
<td>0.7 (0.27, 1.73)</td>
<td>0.1962</td>
</tr>
</tbody>
</table>

**NPI-10**

- 33%

Avec la permission et gracieuseté de BIOGEN
ENGAGE: Longitudinal Change from Baseline in CDR-SB
The primary endpoint of change from baseline in CDR-SB at Week 78 was not met

The ENGAGE trial evaluated the longitudinal change from baseline in CDR-SB in patients with Alzheimer's disease. The primary endpoint was not met at Week 78. The graph shows the adjusted mean change from baseline (±SE) at each analysis visit for Placebo and Low-dose and High-dose aducanumab groups.

Placebo: n=545
Low-dose aducanumab: n=547
High-dose aducanumab: n=554

At Week 78:
- Placebo: 2%
- Low-dose aducanumab: -12%
- High-dose aducanumab: -7%

The data were analyzed using an MMRM model with change from baseline in CDR-SB as the dependent variable and with fixed effects of treatment group, categorical visit, treatment-by-visit interaction, baseline CDR-SB, baseline CDR-SB by visit interaction, baseline MMSE, Alzheimer's disease symptomatic medication use at baseline, region, and laboratory ApoE ε4 status. ITT population. Values at each time point were based on an MMRM model with change from baseline in CDR-SB as the dependent variable and with fixed effects of treatment group.
ENGAGE: Clinical Endpoints at Week 78
Results of the ENGAGE study were partially discordant with those of EMERGE

<table>
<thead>
<tr>
<th>% Difference vs placebo</th>
<th>Low-dose aducanumab</th>
<th>High-dose aducanumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary endpoint</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CDR-SB</td>
<td>-12%</td>
<td></td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(-0.469, 0.110)</td>
<td></td>
</tr>
<tr>
<td>p value</td>
<td>p=0.2250</td>
<td></td>
</tr>
<tr>
<td>MMSE</td>
<td>2%</td>
<td></td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(0.03, -0.262)</td>
<td></td>
</tr>
<tr>
<td>p value</td>
<td>p=0.8330</td>
<td></td>
</tr>
<tr>
<td>ADAS-Cog 13</td>
<td>-6%</td>
<td></td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(-0.62, 0.49)</td>
<td></td>
</tr>
<tr>
<td>p value</td>
<td>p=0.8106</td>
<td></td>
</tr>
<tr>
<td>ADCS-ADL</td>
<td>-11%</td>
<td>-11%</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(-0.583, 0.4181)</td>
<td>(-1.6067, 0.4309)</td>
</tr>
<tr>
<td>p value</td>
<td>p=0.2536</td>
<td>p=0.4795</td>
</tr>
<tr>
<td>Tertiary endpoint</td>
<td></td>
<td></td>
</tr>
<tr>
<td>NPI-10</td>
<td>8%</td>
<td></td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(-2.06, -0.02)</td>
<td></td>
</tr>
<tr>
<td>p value</td>
<td>p=0.1225</td>
<td></td>
</tr>
</tbody>
</table>

*ENGAGE: Clinical Endpoints at Week 78*
*Results of the ENGAGE study were partially discordant with those of EMERGE*

% Difference from placebo (95% CI) p value

- Low-dose aducanumab n=547
- High-dose aducanumab n=555

Avec la permission et gracieuseté de BIOGEN

**Table 1. Clinical trial enrollment criteria and appropriate use criteria for aducanumab in clinical practice**

<table>
<thead>
<tr>
<th>Participant Feature</th>
<th>Clinical Trial Enrollment Criteria</th>
<th>Appropriate Use in Clinical Practice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>50-85</td>
<td>Younger or older patients meeting all other criteria for treatment could be considered candidates for aducanumab</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Clinical criteria for MCI due to AD or mild AD dementia</td>
<td>Clinical criteria for MCI due to AD or mild AD dementia</td>
</tr>
<tr>
<td>Scale scores at baseline</td>
<td>CDR Global Score 0.5; MMSE 24-30; RBANS Delayed Memory Score of 35 or less</td>
<td>MMSE 21-30 or equivalent such as MoCA 17-30</td>
</tr>
<tr>
<td>Amyloid status</td>
<td>Amyloid positive PET (visual read)</td>
<td>Amyloid positive PET (visual read) or CSF findings consistent with AD</td>
</tr>
<tr>
<td>Genetic testing</td>
<td>Consent for APOE genotyping</td>
<td>Genotyping should be discussed with the patient/care partner: ARIA risk should be described, and the patient’s preferences assessed.</td>
</tr>
<tr>
<td>Neurological examination</td>
<td>Non-AD neurological disorders, stroke, and TIA excluded</td>
<td>Non-AD neurological disorders excluded</td>
</tr>
<tr>
<td>Cardiovascular history</td>
<td>Angina; myocardial infarction; congestive heart failure excluded</td>
<td>Stable cardiovascular conditions required; clinical decision can be exercised on the ability of the patient to participate safely with the therapeutic regimen</td>
</tr>
<tr>
<td>Medical history</td>
<td>Excluded: clinically significant systemic illness; diabetes than cannot be managed; uncontrolled hypertension (systolic &gt; 165; diastolic &gt; 100); history of cancer unless in remission for 5 years or localized to skin or prostate; impaired liver function; hepatitis; HIV infection</td>
<td>Stable medical conditions required; clinical decision can be exercised on the ability of the patient to participate safely with the therapeutic regimen</td>
</tr>
<tr>
<td>Psychiatric history</td>
<td>Unable psychotropic illness in the past 6 months; alcohol or substance abuse in the past year; use of cannabinoids; positive urine tests for excluded substances</td>
<td>Must be stable psychiatically; clinical decision can be exercised on the ability of the patient to participate safely with the therapeutic regimen</td>
</tr>
<tr>
<td>Reproductive status</td>
<td>Female subjects who are pregnant or breast feeding excluded; female subjects who are of childbearing age must be practicing contraception</td>
<td>Female subjects who are pregnant or breast feeding excluded; female subjects who are of childbearing age must be practicing contraception</td>
</tr>
<tr>
<td>Clotting status</td>
<td>Bleeding disorders, anticoagulants excluded</td>
<td>Patients on anticoagulants are excluded</td>
</tr>
<tr>
<td>Concomitant medications</td>
<td>Cholesterol inhibitors and anticoagulants allowed</td>
<td>Patients can be on standard of care with cholestelins inhibitors and anticoagulants</td>
</tr>
<tr>
<td>Baseline MRI</td>
<td>Baseline MRI finding that excluded participation: acute or subacute hemorrhage, macrohemorrhage; greater than 4 microhemorrhages, cortical infarction (&gt;1.5 cm), 1 lacunar infarction (&gt;1.5 cm), superficial siderosis, or diffuse white matter disease</td>
<td>Patients should be excluded if there is evidence of acute or subacute hemorrhage, macrohemorrhage, cortical infarction (&gt;1.5 cm), 1 lacunar infarction (&gt;1.5 cm), &gt; 1 area of superficial siderosis, or diffuse white matter disease</td>
</tr>
<tr>
<td>Case support</td>
<td>Reliable informant or care partner</td>
<td>May be living independently or with a care partner</td>
</tr>
<tr>
<td>Informed consent</td>
<td>Must be signed by participant and care partner</td>
<td>Patient and care partner must understand the nature and requirements of therapy (e.g. monthly infusions to be performed indefinitely) and the expected outcome of therapy (showing decline of clinical features)</td>
</tr>
</tbody>
</table>

**Abbreviations:** AD – amyloid beta protein; AD – Alzheimer’s disease; APOE – apolipoprotein E; CDR – Clinical Dementia Rating; cm – centimeter; CSF – cerebrospinal fluid; HIV – human immunodeficiency virus; MMSE – Mini Mental State Examination; MoCA – Montreal Cognitive Assessment; MRI – magnetic resonance imaging; PET – positron emission tomography; RBANS – Repeatable Battery for the Assessment of Neuropsychological Status; TIA – transient ischemic attack
POLLING QUESTION NO 4: TRUE OR FALSE?

The CDR-SB will be the main tool to follow patients with MCI due to AD undergoing anti-amyloid therapies.
Reduction of amyloid plaque levels was maintained during the treatment gap from the end of feeder studies to EMBARK baseline: Pooled EMERGE/ENGAGE substudy data and PRIME data.
Aducanumab significantly lowers plasma p-tau$^{181}$

**EMERGE**

- **Baseline Mean (pg/ml):**
  - Placebo: 3.19
  - Low: 3.27
  - High: 3.35

- **Analysis visit (weeks):**
  - 0: Placebo 287, Low dose 293, High dose 290
  - 56: Placebo 177, Low dose 172, High dose 168
  - 78: Placebo 273, Low dose 269, High dose 271

**ENGAGE**

- **Baseline Mean (pg/ml):**
  - Placebo: 3.18
  - Low: 3.24
  - High: 3.11

- **Analysis visit (weeks):**
  - 0: Placebo 333, Low dose 331, High dose 281
  - 56: Placebo 301, Low dose 299, High dose 242
  - 78: Placebo 325, Low dose 322, High dose 274

---

*p<0.05, **p<0.01, ***p<0.001 compared with placebo (nominal). MMRM with change from baseline as the dependent variable and with fixed effects of treatment group, categorical visit, treatment-by-visit interaction, baseline value, baseline value by visit interaction, baseline age, and ApoE status. ApoE, apolipoprotein E; MMRM, mixed model for repeated measures; pg/ml, picograms per milliliter; p-tau, phosphorylated tau; SE, standard error.
EMERGING GUIDELINES FOR ANTI-AMYLOID DRUGS - 1

• They would help in ‘early AD’ (MCI and mild dementia due to AD, e.g. A+)
• They need high doses with risk of ARIA (brain swelling and micro bleeds)
• They may have downstream effect on tau pathological spread
EMERGING GUIDELINES FOR ANTI-AMYLOID DRUGS -

• It may be possible to stop the Rx after reaching A- as demonstrated by PET, CSF or plasma ptau

• They should be stopped when reaching moderate dementia, which may be operationally defined as CDR-global 2, MMSE below 19, loss of IADL.
POLLING QUESTION NO 4: TRUE OR FALSE?

The CDR-SB will be the main tool to follow patients with MCI due to AD undergoing anti-amyloid therapies.

FALSE
NATURAL HISTORY OF AD AND CURRENT Rx

No standard drug therapy

Normal

MCI

Antidepressants, Cls

ANTI-AMYLOID Rx if A(+)

Early

Cls

Memantine

Memantine; Cls

Atypical neuroleptics

Moderate

Severe

Memantine; Cls

Atypical neuroleptics

Terminal

Temps (ans)
CONCLUSIONS

• The diagnosis of MCI and dementia due to AD is becoming biological but should done in symptomatic people with demonstrated cognitive decline.

• The COVID-19 pandemic has accelerated the use of telemedicine, including remote cognitive assessments – possibly a golden age for remote cognitive screening for MCI.

• MCI due to AD has become a target for disease modifying therapies and will require in-person and remote cognitive & functional follow-up.
REFERENCES


• Li et al. Concordance between the clinical and the electronic CDR. J Prev Alz Dis 2021;8(S1):S30-31